HER2-targeting antibody-drug improves progression-free survival for women with deadly form of advanced breast cancer

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A study led by researchers at the UCLA Jonsson Comprehensive Cancer Center has found that treating women with HER2 positive metastatic

breast cancer with the HER2-targeting antibody-drug conjugate trastuzumab deruxtecan (T-DXd) significantly prolongs the length of time the disease is controlled and cancer growth is halted when compared to the current standard of care, trastuzumab emtansine (T-DM1).

The drug T-Dxd is comprised of a HER2-targeted monoclonal antibody that delivers high concentrations of chemotherapy directly to cancer cells that have HER2 on their surface. Patients who received the drug had a 72% improvement in progression-free survival compared to T-DM1.

When compared at the 12-month mark, 76% of patients who were treated with T-DXd had not yet had their disease progress, meaning their disease remained under control. For those treated with T-DM1, only 34% of patients did not see their disease progress by 12-months.

"It was a really substantial difference in the two treatment arms," said senior author Dr. Sara Hurvitz, director of the Breast Cancer Clinical Research Program at the UCLA Jonsson Comprehensive Cancer Center. "This data is nothing short of phenomenal and will be practice changing."

The results (LBA1) from the clinical trial are featured in the Presidential Symposium at the European Society for Medical Oncology Congress (ESMO). This is the first phase III trial to report a comparison in the safety and efficacy of T-Dxd versus a standard therapy in metastatic breast cancer.

Currently, the first-line standard of care for patients with HER2-positive metastatic breast cancer is HER2 antibody therapy with pertuzumab/trastuzumab, plus chemotherapy. If the cancer progresses, the standard care is to switch therapy to T-DM1, which is an antibody-drug conjugate comprised of trastuzumab and chemotherapy.

Up to 20% of breast cancers are classified as HER2 positive, meaning the tumor has extra copies of the gene for HER2 and too much HER2 protein on the cell surface, which in turn causes the cancer to behave more aggressively, leading to worse outcomes including a higher chance of metastases, or spread throughout the body. The development of HER2-targeted treatments such as trastuzumab, pertuzumab, and T-DM1 have greatly improved outcomes, including survival, associated with this disease. However, the majority of patients with advanced disease will experience disease resistance and progression, despite having these targeted therapies.

Promising new drugs have emerged as effective options for these patients, including T-DXd, which received accelerated approval by the US Food and Drug Administration in 2019 for patients with unresectable or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2-based regimens in the metastatic setting. This approval was based on a smaller, non-comparative trial, DESTINY-Breast01, that demonstrated very promising efficacy in patients whose disease had progressed after T-DM1.

The results from the newly reported clinical trial, called DESTINY-Breast03, shows that T-DXd, is significantly better than T-DM1 when used after a patient's disease has progressed on trastuzumab and chemotherapy.

"T-DM1 became the standard of care second-line therapy in 2013 and is the first FDA approved antibody drug conjugate. It has a solid safety and efficacy profile," said Hurvitz, who is also a professor of medicine at the David Geffen School of Medicine at UCLA. "In the past eight years we have not seen any other therapy try to beat it in a head-to-head trial. Seeing a new therapy demonstrate such a substantial improvement in progression free survival compared to T-DM1 is really exciting for our patients."

The DESTINY-Breast03 trial included 524 patients who were randomized to either the T-DXd arm or the comparator T-DM1 arm. Median age of participants was 54 and ranged from 20-83. All were previously treated with trastuzumab and chemotherapy before starting the clinical trial.

Along with a longer progression-free survival in the T-DXd arm, almost 80% of patients saw their tumors shrink compared to only 34% treated with T-DM1. And 16% of T-DXd treated patients had their diseases completely disappear.

The safety profile was consistent with other reported data regarding T-DXd. Treatment-related interstitial lung disease was observed in 10.5% of patients, with most (9.7%) categorized as grade1/2. There were no grade 4/5 treatment-related interstitial lung disease events observed and no drug-related deaths occurred in either arm.

The next step is to study T-DXd in the front-line metastatic setting and in early stage disease. At the UCLA Jonsson Comprehensive Cancer Center, Hurvitz is investigating how well T-DXd works alone or in combination with anti-estrogen therapy, in treating patients with HER2 low, hormone receptor positive breast cancer (NCT04553770).

Other investigators are Javier Cortés, Sung-Bae Kim, Wei-Pang Chung, Seock-Ah Im, Yeon Hee Park, Roberto Hegg, Min-Hwan Kim, Ling-Ming Tseng, Vanessa Petry, Chi-Feng Chung,Hiroji Iwata, Erika Hamilton, Giuseppe Curigliano, Binghe Xu, Caleb Lee, Yali Liu, Jillian Cathcart, Emarjola Bako and Sunil Verma.

Provided by University of California, Los Angeles

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